1 Introduction

Alzheimer's disease (AD) is a debilitating medical condition that affects one in eight people over 65 years old [**?**]. However, precise details of the mechanism that causes AD are largely unknown. Here we build a graph theoretic model that demonstrates the importance of symmetry of the cerebral arterial tree to the proliferation of AD.

1.1 Medicine

Extracellular space in the brain contains interstitial fluid (ISF) which is produced by the blood and by-products of cell metabolism. The extracellular spaces within the walls of cerebral blood vessels referred to as *basement membranes* and represent the perivascular pathways along which ISF drains out of the brain [**?**, **?**, **?**].

Figure 1: Perivascular drainage of Aβ.

The walls of cerebral capillaries consists of one fused layer of the basement membrane which is approximately 150 nm in thickness.

Alzheimer's disease is the commonest dementia - characterised by serious and progressive cognitive decline and appears to be due to a failure of elimination of amyloid-β (Aβ) from the brain. Aβ is a normal by-product of cell metabolism produced at all ages [].

One mechanism for the removal of Aβ from the brain parenchyma is perivascular drainage, by which Aβ within ISF enters the capillary basement membranes draining to the walls of arteries towards the surface of the brain [**?**][**?**]. With ageing and certain genetic background soluble Aβ is not eliminated from the brain and it is deposited in the walls of blood vessels as cerebral amyloid angiopathy (CAA) [**?**].

Figure 2: CAA in a leptomeningeal artery.

The deposition of Aβ in the perivascular spaces in the blood vessel walls can cause a further blockage of the ISF drainage pathways resulting in an alteration of the composition of ISF in the brain parenchyma. This change in biochemical composition of the ISF leads to nerve cell death and Alzheimer's Disease. [**?**].

CAA is most prominent in the occipital, temporal and frontal lobes and least prominent in the parietal lobe and cerebellum. In particular, the leptomeningeal and cortical arteries are particularly prone to CAA whereas CAA is very rare in capillaries [**?**]. One possible reason for the differing expected degrees of CAA could be the differing topology and symmetry of the cerebral arterial tree. In order to test this hypothesis we consider a graph theoretic model of CAA therefore we need to make some relevant definitions from graph theory.

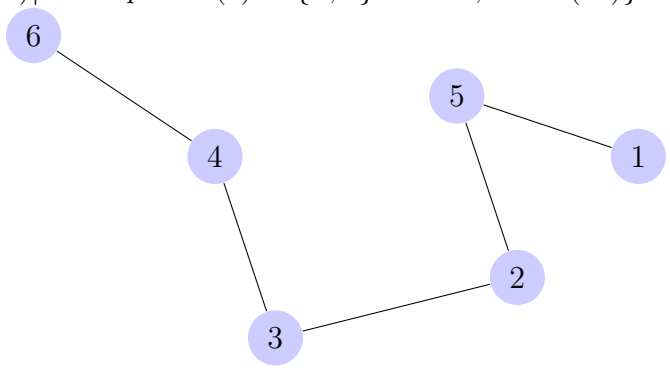
1.2 Graph Theory

The references for this section are [**?**] and [**?**]. Graph Theory has been an established area of discrete mathematics since 1736 when Euler solved the famous question regarding the bridges of Königsberg. More recently, in the 1940s and 50s Erdős and Rényi laid the foundations of the theory of random graphs seeking to answer fundamental questions about the nature of "most" graphs.

Random graphs have been studied for their own sake and have been used to model a diverse set of real-world networks from the world wide web to the metabolism of *E. coli* [**?**]. Recently, the advent of the world wide web and the accompanying (relatively) cheap and powerful computational power has led to a reemergence of graph and random graph theory under the guise of "Network Science".

An simple undirected graph, G, is a pair $G = (V(G), E(G))$ where $V(G)$ is the a set of vertices or nodes of the graph and $E(G)$ is the set of edges of G. Each edge $e \in E(G)$ has two endpoints $u, v \in V(G)$ and we say that if $e = e_{u,v}$ then u and v are *adjacent* and that $endpoints(e) = \{u, v\}$. We do not allow more than one edge between a pair of vertices or loops which are edges e such that $endpoints(e) = \{u\}$. The degree of any vertex v is the number of edges e such that $v \in endpoints(e)$.

A tree, T, is a graph such that the shortest path between any pair of vertices $u, v \in V(T)$ is unique. One can consider the *induced subtree*, T' of tree T where $V(T') \subset V(T)$ and $E(T') = \{e \in E(T) |$ if $endpoints(e) = \{u, v\}$ then $u, v \in V(T')\}$.



A *random recursive tree* (RRT), T, with vertices $V(T) = \{v_1, \ldots, v_n\}$ is a labelled, rooted tree obtained by assigning a root vertex v_1 then adding $n - 1$ vertices one by one such that each new vertex is joined by an edge to a randomly and uniformly chosen existing vertex. A random recursive q-ary tree is a labelled, rooted tree built in the same way as a random recursive tree except each new vertex is attached uniformly at random to an existing vertex that has outdegree less than q [**?**]. We say that RRTs and random recursive q-ary trees are *increasing* trees.

Given an increasing tree T_n on n vertices labelled by the function $\phi : V(T) \to \{1, 2, \ldots, n\}$ and a vertex $v \in V(T)$ then we can consider $\tilde{T}_v$ which is the induced subtree with vertices, $v_i \in B(v)$ such that $\phi(v_i) \geq \phi(v)$.

Given some tree T we can formally measure how *symmetric* that tree is by calculating the number of permutations of the vertices of that graph which preserves adjacent vertices. We call the set of all these permutations, $Aut(T)$, the *automorphism group* of T and the number of allowed permutations, $|Aut(T)|$ is the size of the automorphism group.

Example 1.1. Consider the following increasing tree T_{14} with 14 vertices.

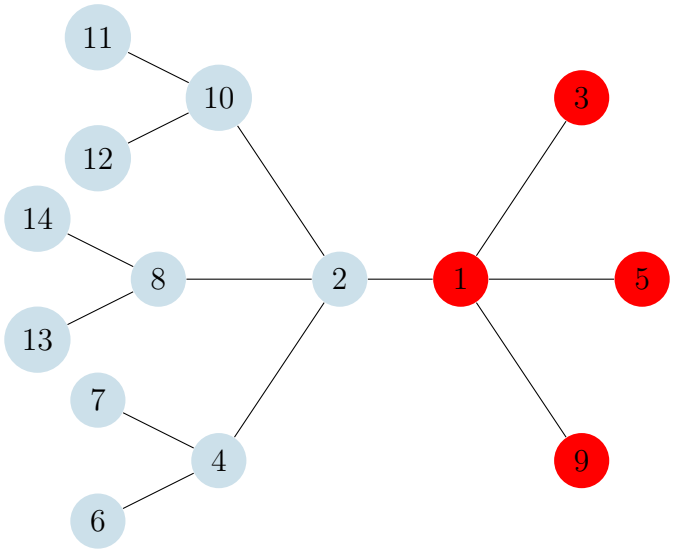


Figure 3

The red vertices in Figure **??** indicate an induced subtree $\tilde{T}_{v_1}$. We can permute the vertices v_3, v_5 and v_9, for example the following is a valid permutation of these vertices.

$$3 \to 5$$
$$5 \to 3$$
$$9 \to 9$$

Note that after the above permutation all three vertices remain adjacent to v_1. There are $3! = 6$ distinct such permutations. The blue vertices in Figure **??** highlight an extended symmetric induced subtree, $\tilde{T}_{v_2}$. We can permute any of the pairs $\{v_6, v_7\}, \{v_{11}, v_{12}\}$ and $\{v_{13}, v_{14}\}$ and we can permute the longer branches. For example the following is a valid (adjacency preserving) permutation:

$$4 \to 8$$
$$6 \to 13$$
$$7 \longrightarrow 14$$
$$8 \to 4$$
$$13 \to 7$$
$$14 \to 6$$

Where every other vertex is fixed. There are X possible valid permutations of the blue vertices, therefore $|Aut(T_{14})| = 6 \times X = 6X$

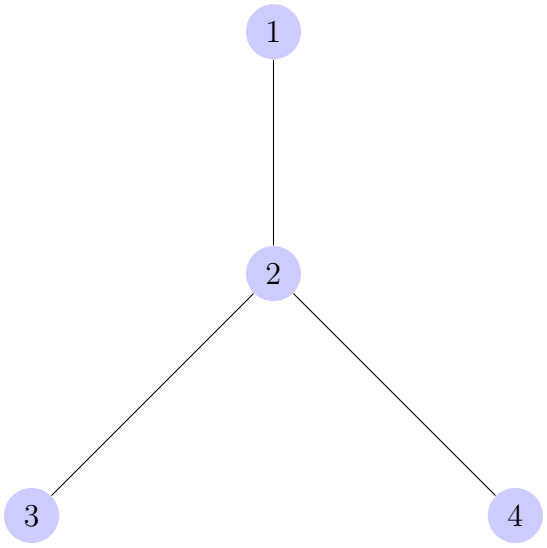


Figure 4: Perivascular drainage of Aβ.

1.2.1 Anatomical Data

In order to build an effective model we require anatomical data such as the expected length and radii of arterial vessels and the expected number of branching points.

Note that 98% of branching in the cerebral cortex is bifurcation and we expect approximately 300 branching points [**?**].

Murray's principle of minimization of operational cost says that the cost of operation of physiological systems tends to a minimum. One consequence of Murray's principle is referred to as Murray's law which states that for 2 daughter branches d_1 and d_2 from a common parent arterial vessel, p:

$$r_p^3 = r_{d_1}^3 + r_{d_2}^3$$

where r_p is the radius of p and r_{d_1}, r_{d_2} are the radii of d_1 and d_2 [**?**]. Experimental evidence has shown that Murray's law is a good approximation for arterial vessels [].

Murray's law describes the relationship between particular vessels which can be thought of as *cylinders*. However, recall that our goal is to model the cerebral perivascular pathways which can be thought of as *annular prisms*. Therefore we will adjust Murray's law to describe the relationship between parent and child annular prisms. Since the notion of radius is more complicated for an annular prism it is appropriate to reformulate Murray's law in terms of cross-sectional area.

We assume that the width of the perivascular space, ϵ is the same for any vessel from capillary to artery. So let he parent vessel have radius $r_p = r'_p + \epsilon$ and the two daughter vessels have radii $r_{di} = r'_{di} + \epsilon$. The relationship between the cross-sectional area, A_X of any vessel and the radius,

r_X of that vessel is given by the formulae:

$$A_X = \pi((r'_X + \epsilon)^2 - r'^2_X) \tag{1}$$
$$= \pi(\epsilon^2 + 2\epsilon r'_X) \tag{2}$$
$$r'_X = \frac{A_X - \pi\epsilon^2}{2\epsilon\pi} \tag{3}$$
$$r_X = \frac{A_X - \pi\epsilon^2}{2\epsilon\pi} + \epsilon \tag{4}$$
$$= \frac{A_X + \pi\epsilon^2}{2\epsilon\pi} \tag{5}$$

By combining the above equations we find that the cross-sectional area of the parent vessel, A_p, is given by:

$$A_p = \pi(\epsilon^2 + 2\epsilon r_p) \quad = \pi\left(\epsilon^2 + 2\epsilon(r_{d_1}^3 + r_{d_2}^3)^{\frac{1}{3}}\right) = \pi\left(\epsilon^2 + 2\epsilon\left(\left(\frac{A_{d_1} + \pi\epsilon^2}{2\epsilon\pi}\right)^3 + \left(\frac{A_{d_2} + \pi\epsilon^2}{2\epsilon\pi}\right)^3\right)^{\frac{1}{3}}\right) \tag{6}$$

where A_{d_1} and A_{d_2} are the cross-sectional areas of the two daughter vessels.

2 What we did

We developed a program in Matlab [] to model the role of symmetry in perivascular drainage. Firstly we built 50 random trees with 300 nodes and maximum valency 3. These were obtained by beginning with a pair of nodes connected by an edge then at time t a new edge connects node labelled t to one of the existing nodes with valency less than 3 uniformly at random.

We then associated a capacity to each edge in the following way:

(i) An edge with an endpoint that is a leaf is given capacity/volume 1 corresponding to radius $\frac{1}{\sqrt{\pi}}$.

(ii) We assume that all edges have length 1 and apply Murray's law for annuli to generate all other capacities.

For each tree T we used nauty [**?**] to calculate $aut(T)$.

We then activate our model by using the discrete variable t where initially $t = 0$ and subsequently $t = 1, 2, 3, \ldots$.

We define a variable, v, related to concentration.

$$v = initialcapacity/currentcapacity$$

As our model develops the capacity of the whole tree decreases because parts become "clogged up" so v is monotonically increasing.

At each discrete time with probability proportional to v we remove an edge and the induced subtree of v. This replicates CAA an amyloid plaque in a branch.

We also record the time at which every edge has been removed from tree T which we will refer to as the silting time.

Finally we split the trees into the 25 trees with largest automorphism group and 25 trees with smallest automorphism groups and recorded the mean

3 Results

add my diagram.

We see that more symmetric trees take longer to fully silt (on average).

3.1 Interpretation of results

Now we translate the mathematics back to biology. Is it expected that more symmetric trees are more robust to this kind of attack?

Is there corroborating evidence from places who knows where!.

4 Further Directions

what about angiogenisis - Ambrose

stiffening of arteries over time - radial function decreases. Note that in the future lengths chosen from a probability spectrum would improve the matter.